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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/763,340	01/23/2004	Timothy A. Hagen	PC25240A	7074

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PFIZER INC.
PATENT DEPARTMENT, MS8260-1611
EASTERN POINT ROAD
GROTON, CT 06340

EXAMINER	
HAWES, PILI ASABI	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 07/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/763,340	HAGEN ET AL.	
	Examiner	Art Unit	
	Pili A. Hawes	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16,25-38,49-65 and 76-91* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16,25-38,49-65 and 76-91* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Summary

Receipt of Applicant's response to the Office Action mailed 05-23-2005 is acknowledged. Claims 17-19, 21-24, 39-48 and 66-75 have been cancelled. Claims 16, 25-38, 49-65, and 76-91 are pending in this action. Claims 16, 25-38, 49-65, and 76-91 are rejected.

Priority

Applicant's submission of the Application Data Sheet is acknowledged. Applicant's amendment to the specification to include reference to prior application 60/527084 is appreciated. Applicant has met the requirement for priority and the objection has been withdrawn.

Specification

Applicant's amendment to the specification to include the missing U.S. Patent Application Serial Numbers, and to delete the legal phraseology in the abstract is acknowledged. The objection to the specification is withdrawn.

Claim Objections

Applicant's amendment to claims 34 and 87 to remove improper dependence is acknowledged. The objection to the claims is therefore withdrawn.

Claim Rejections - 35 USC § 102

The 35 USC 102 (b) rejection to claims 16-18, 21-23, 36, 49-55, 60, 61-68, 70-73, 76-82, 87, 90 and 91 over Curatolo et al. US 6068859 has been withdrawn due to

applicants amendment to claim 16 and the cancellation of claims 17-18, 21-23, 66-68, and 70-73. Due to applicant's amendment Curatolo et al. no longer anticipates the instant claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 16 is rejected for containing improper Markush language. Amendment of claim 16 (ii) is suggested to the following format:

"about 25% to about 80% of a glyceride wherein the glyceride is glyceryl monobehenate, glyceryl dibehenate, glyceryl tribehenate, or a mixture thereof," **or**

"about 25% to about 80% of a glyceride wherein the glyceride is selected from the group consisting of glyceryl monobehenate, glyceryl dibehenate, glyceryl tribehenate, and a mixture thereof".

Response to Arguments

Applicant's arguments with respect to claims 16, 25-38, 49-65, and 76-91 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 16, 25-38, 49-65, and 76-91 are rejected under 35 U.S.C. 103(a) as being obvious over Curatolo et al. US 6068859 (Curatolo) in view of WO 03/032922 (WO) and further in view of Constantinides et al. US 6479540 B1 (Constantinides) and Maggi et al. US 6221395 B1.

Curatolo discloses an oral dosage form of azithromycin comprising an alkalizing agent, a wax, and a glyceride (col. 7, 15-47). Curatolo discloses modified vegetable oils, carnauba wax, hydrogenated castor oil, and beeswax (col. 7, 30-32). The reference also discloses the use of a dissolution agent, such additives are sugars, salts, soluble polymers, and alcohols (col. 8, 49-55). Sodium lauryl sulfate is disclosed in the tablet core formulation in Table 31 (col. 54, 22-35). Table 31 also discloses azithromycin is in the from of a dihydrate as is claimed in claim 36. Table 31 also discloses a phosphate alkalizing agent, specifically calcium phosphate dibasic. The oral dosage formulation disclosed in the prior art yields lower incidence of gastrointestinal side effects (col. 1, 50-58). The prior art also discloses a method of treating microbial infections using the azithromycin formulation (col. 1, 13). The oral formulation administered to a human (col. 1, 15). Example 1 discloses a single 2 g oral dose of azithromycin being administered

(col. 29, 15-20). Example 15 discloses comparative example of an immediate release and delayed release formulation of azithromycin (col. 45, 30-60). Curatolo suggests that the formulation disclosed could be used in children stating that rates of release of azithromycin in "patients under 50 kg weight, e.g. children" may be better than the rate of release in adults.

Curatolo does not teach all the glycerides listed by applicant. Specifically, the reference does not disclose the use of glyceryl behenate. Curatolo does not disclose the use of poloxamer 407 as a dissolution enhancer. Curatolo also does not disclose the use of magnesium hydroxide and tribasic sodium phosphate as the alkalizing agents.

WO 03/032922 discloses azithromycin powder formulations that contain sodium lauryl sulfate, anti-foaming agents, sweeteners and fillers, and pH buffers (pages 9-10). The reference teaches the specific glyceride, glyceryl behenate (page 8). WO also teaches tribasic sodium phosphate as an additive to maintain pH (page 10). WO does not disclose the use of poloxamer 407.

Constantinides teaches a number of the dissolution agents claimed by applicant (col. 7, 60-67). The reference specifically discloses pharmaceutical formulations comprising poloxamer 407 in combination with macrolide antibiotics such as clarithromycin and erythromycin (col. 9-10). Constantinides teaches poloxamers are surfactants (col. 7, 67). The reference also discloses that azithromycin is a member of the macrolide antibiotic class of drugs (col. 9, 7). Constantinides teaches that macrolide

antibiotics are primarily administered orally due to venous irritation when administered as an injection (col. 9, 8).

Maggi et al. discloses a pharmaceutical preparation for poorly water soluble drugs, that can be adapted to make fast or slow release formulations (abstract). Maggi teaches the use of poloxamer (col. 3, line 51) as a surfactant which is used to modulate the release of the active ingredient (col. 3, line 27-32). The reference also teaches the use of other pharmaceutical excipients, such as mono-bi-tri-substituted glycerides that can be added in order to slow the penetration of water or aqueous fluids in the treated layer of the composition (col. 4, lines 46-54). Maggi specifically teaches glyceryl behenate as a pharmaceutical excipient that can be added in the formulation (col. 4, line 40). Example 7 discloses the glyceryl behenate is added 18.41 % by weight to the composition (col. 9, line 53). This percentage make obvious the range "about 25-80%" because applicants definition of the term "about" is ± 10% of the limit of the range.

It would have been *prima facie* obvious to one of ordinary skill in the art to add glyceryl behenate, tribasic sodium phosphate (WO), and poloxamer 407 (Constantinides) into the invention of Curatolo because glyceryl behenate and poloxamers are used commonly in the art as release modifiers, and buffers such as inorganic bases can enhance solubility and release of an active agent in an aqueous environment. One of ordinary skill in the art would be motivated to use lubricants such as glyceryl behenate in making controlled released dosage formulations because Maggi teaches that the addition of glycerides can slow the penetration of water into the formulation, such as would be useful in a controlled release formulation. One would be

motivated to add pH buffers such as tribasic sodium phosphate because it would allow for elevation of the pH, which would decrease gastrointestinal side effects and act as a buffering agent that could increase the solubility of an azithromycin salt, such as azithromycin dihydrate, which is soluble above neutral pH. One of ordinary skill in the art would be motivated to add poloxamers to the formulation because poloxamers are surfactants that are able to be combined with macrolide antibiotics and enhance solubility and modify the release of the antibiotic.

Tribasic sodium phosphate and magnesium oxide are both alkalizing agents. Absent a showing of criticality for the combination of these particular alkalizing agents, the prior art already teaches the use of alkalizing agents in an azithromycin formulation. It is within the realm of one of ordinary skill in the art to be able to select the specific alkalizing agents or combination of alkalizing agents to make the specific formulations desired.

Claims 16, 25, 26, 28-30 and 38 is rejected under 35 U.S.C. 103(a) as being unpatentable over Appel et al. US 6706283 B1 in combination with Constantinides et al. US 6479540 B1 (Constantinides).

Appel discloses controlled release oral dosage forms of poorly soluble active agents (col. 2, lines 64-67). Appel lists azithromycin as an example of macrolide antibiotics that are suitable for incorporation into the dosage form (col. 7, line 37). Appel also teaches the addition of excipients such as dicalcium phosphate and other inorganic bases as solubility enhancing agents (col. 12, lines 18 and 25). Appel also teaches the desirability of adding other solubilizing excipients such as polyethylene oxide-

polypropylene oxide block co-polymers (poloxamers) in the formulation (col. 15, line 65). Appel also teaches the addition of 50% by weight glyceryl behenate and 25% by weight drug dispersion (col. 27, lines 3-4).

Appel does not disclose the use of the specific poloxamer, poloxamer 407.

As disclosed above, Constantinides teaches a number of the dissolution agents claimed by applicant (col. 7, 60-67). The reference specifically discloses pharmaceutical formulations comprising poloxamer 407 in combination with macrolide antibiotics such as clarithromycin and erythromycin (col. 9-10). Constantinides teaches poloxamers are surfactants (col. 7, 67). The reference also discloses that azithromycin is a member of the macrolide antibiotic class of drugs (col. 9, 7). Constantinides teaches that macrolide antibiotics are primarily administered orally due to venous irritation when administered as an injection (col. 9, 8).

One of ordinary skill in the art would be able to determine through routine experimentation the desired amounts of active ingredient to add to the formulation to achieve the desired concentration of active agent in the dosage form.

It would be obvious to one of ordinary skill in the art to use the specific poloxamer taught by Constantinides in a formulation with a macrolide antibiotic such as azithromycin because poloxamers are dissolution enhancers and help to modify the release of the active agent in the formulation. One would be motivated to use the poloxamer 407 because azithromycin is poorly water-soluble and the poloxamer enhances solubility.

Conclusion

Claims 16, 25-38, 49-65, and 76-91 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Pili A. Hawes whose telephone number is 571-272-8512. The examiner can normally be reached on 8-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page can be reached on 571-272-0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

P.A. Hawes
Examiner-1615

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600